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Original Article

Clinical Features and Culprit Food Allergens of Korean Adult Food Allergy Patients: A Cross-Sectional Single-Institute Study

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ABSTRACT

Purpose: To investigate the causative allergens and clinical characteristics of Korean adult patients with food allergy (FA).
Methods: This retrospective, cross-sectional single-institutional study enrolled Korean adult patients (n = 812) suspected of having FA. For diagnosis, causality assessment history taking, ImmunoCAP specific immunoglobulin E measurement and/or skin prick test were performed.
Results: Among 812 patients, 415 were diagnosed as having FA. The most common causative allergen was fruit, with a diagnosis of pollen food allergy syndrome (PFAS: 155, 37.3%), followed by crustaceans (111, 26.7%), wheat (63, 15.1%), fruits in patients without PFAS(43, 10.3%), buckwheat (31, 7.4%), peanut (31, 7.4%), walnut (25, 6.0%), red meat due to reaction to galactose-α-1,3-galactose (α-Gal) (8, 1.9%), and silkworm pupa (13, 3.1%). Allergy to egg, milk, fish, or shellfish was rare in Korean adults. One-third of patients with FA exhibited multiple FAs (238/415, 57.3%); the average number of causative allergens was 2.39. About 129 patients (31.0%) were diagnosed as having anaphylaxis; in these patients, wheat was the most frequent causative food. Twenty patients were further diagnosed with food-dependent exercise-induced anaphylaxis (FDEIA); all were due to wheat. In particular, crustaceans, wheat, PFAS, buckwheat, and red meat (α-Gal) were also frequent causes of anaphylaxis.
Conclusions: Wheat, fruits with or without PFAS, and crustaceans are important and frequent causative allergens in Korean adult FA; these allergens differ from those found in childhood FA. It is notable that non-classic allergies, such as PFAS, FDEIA, and α-Gal allergy, are the important causes of anaphylaxis in Korean adult FA.

Keywords: Adults; food allergy; food allergen; anaphylaxis; Korea

INTRODUCTION

Food allergy (FA) is an emerging public health problem that affects up to 10% of the worldwide population.[1] In Korea, with changes in dietary habits, the prevalence of allergic diseases has increased. Accordingly, public concern regarding FA is continuallygrowing.[2-6]

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Disclosure

All authors have no potential conflicts of interest to disclose.

As common foods differ between Western and Eastern Asian countries, the causative food allergens may also differ. However, the prevalence of FA is about two times higher in adults than in children; the total number of adult FA patients outnumbers that of pediatric FA patients.[7,8] Nonetheless, most studies on the prevalence of FA in Korea focus on pediatric patients. Therefore, improved understanding of current clinical features of Korean adult FA is important for the diagnosis of adult FA, patient and public education, and making public health regulations related to FA.[4]

FAs are primarily classified into immunoglobulin E (IgE)-mediated and non-IgE-mediated, based on the mechanism, and subordinate specific disorders can be diagnosed based on the clinical manifestations. Among IgE-mediated FAs, pollen food allergy syndrome (PFAS), food-dependent exercise-induced anaphylaxis (FDEIA), and galactose-α-1,3-galactose (α-Gal) allergy can be considered as special subtypes due to different clinical features and causative allergens.[9,10]

Previously, several studies revealed the epidemiology of adult FA in Korea.[11,14] However, as the study sample was relatively small, their findings may not represent nationwide trends; moreover, patients differed by institution and region. Furthermore, specialized FA subtypes were not included. Accordingly, we aimed to analyze the common causative allergens of adult FA in a single tertiary university hospital in Korea, focusing on clinical manifestations and implications.

MATERIALS AND METHODS

Study design and patient selection

We retrospectively reviewed the medical records of 812 Korean adult patients with suspected FA and who visited the Allergy Asthma Center of a tertiary hospital in Korea from January 2014 to December 2018. Among the patients, we enrolled those who had plausible clinical features, adequate temporal relationships, causal specificity, reproducibility between specific food ingestion and symptom(s) occurrence, and confirmation of causative food allergen-specific IgE (sIgE) with immunologic tests, such as multiplex allergen specific immunoassays or skin prick test (SPT). Suspected culprit food allergens were double-checked using a singleplex sIgE test. A revised version of the Bradford and Hills criteria was applied to establish causality between causative food(s) and FA.[15] This study was reviewed and approved by the Institutional Review Board of Severance Hospital (approval No. 2018-3109-001).

Food allergens

Seventy food items were evaluated as causative food allergen(s) (**Table 1**). Because of food allergen diversity, we grouped food allergens by their origins as per the food classifications from the Ministry of Health, Labour and Welfare of Japan. Some unique food allergens, such as *dorajī* (balloon flower root), ginseng, *ma* (Chinese yam), and *sseumbagui* (Korean lettuce), which are frequently consumed in Korea, were also added to the allergen lists.

Severity classification

FA severity was classified as mild, moderate, or severe. Mild symptoms were defined as a single symptom that did not require medical intervention. Moderate symptoms were defined as symptoms requiring light medical intervention, such as oral medication or face-to-face medical advice. Severe symptoms were defined as anaphylaxis, which was diagnosed based on clinical features consistent with the World Allergy Organization anaphylaxis diagnosis guideline.[16]

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Table 1. Food allergens classified by their origins

Class	Type	Group	Food
Plant origin	Cereal grains and legumes	Legumes	Peanut soybean, pea
		Cereal grains	Wheat, buckwheat, rice, barley grain, gluten
	Nuts and seeds	Tree nuts	Walnut, almond, cashew nut, sweet chest nut, hazelnut
		Seeds	Sesame, pine nut, sunflower seed, cacao
	Other vegetables	Potatoes	Potato, sweet potato
		Cruciferous veg	Cabbage, broccoli
		Composite veg	Lettuce
		Liliaceous veg	Garlic
		Umbelliferous veg	Carrot, celery
		Solanaceous veg	Tomato
		Cucurbitaceous veg	Cucumber, watermelon, melon, Makuwa melon
		Mushrooms	Mushroom
	Fruits	Pome fruits	Apple, pear
		Citrus fruits	Orange
		Stone fruits	Peach, plum, cherry
		Grape	Grape
		Berries	Strawberry
		Assorted tropical and subtropical fruits	Kiwi, mango, persimmon, banana, avocado, pineapple
Animal origin	Terrestrial mammals	Red meat	Pork, beef
	Poultry	White-meat	Chicken
	Aquatic animals	Fish	Mackerel, codfish, herring, eel, anchovy, tuna, salmon
		Crustacean	Crab, shrimp, lobster
		Shellfish	Clam, oyster
		Cephalopod	Squid
	Eggs of poultry		Egg
	Milk and dairy products		Milk, cheese
Miscellaneous		Yeast, ginseng, silkworm pupa (chrysalis), *doraji* (balloon flower root), *ma* (Chinese yam), *sseumbagui* (Korean lettuce)	

Veg, vegetable

Diagnostic studies

An SPT was routinely performed using commercial extracts (Allergopharma, Reinbek, Germany). A positive SPT reaction was defined when the mean wheal diameter of the allergen response was larger than 3 mm compared to that of a negative control.[17] Some food items (silkworm pupa [chrysalis], common eel [*Anguilla japonica*], anchovy [*Engraulis japonicus*], squid [*Todarodes pacificus*], and mackerel [*Scomber japonicus Houttuyn*]) are not commercially available, but are frequently consumed food allergens; these were prepared at the Yonsei allergy institute. To manufacture new SPT reagents, allergen extracts were prepared as previously described.[12] AdvanSure™ AlloScreen (LG Life Science, Seoul, Korea) assay was used for multiplex sIgE detection. Results of multiplex sIgE test using AlloScreen were classified into 7 levels ranging from classes 0 to 6. Reactions of class 2 (≥ 0.70 IU/mL) or higher were considered positive.[18,19] Singleplex allergen-sIgE levels were measured using ImmunoCAP (Thermo Fisher Scientific/Phadia, Uppsala, Sweden); levels >0.35 kU/L were regarded as positive.[13,20] All tests were carried out according to the standard instructions. There were several allergens, such as sunflower seed, sweet potato, lettuce, Makuwa melon, mushroom, and persimmon, for which immunoCAP testing could not be performed. For these allergens, FA was diagnosed by history taking and other immunologic tests (SPT or multiple allergen simultaneous test). For food items without any commercially available diagnostic test, such as *doraji*, ginseng, *ma*, and *sseumbagui*, FA was diagnosed according to clinical features based on revised Bradford and Hills criteria for establishing causality relation.[15]

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Identifications of PFAS

Among the study subjects, comorbid PFAS was diagnosed if the following criteria were met: 1) presence of comorbid allergic rhinitis (AR), allergic conjunctivitis, and/or bronchial asthma; 2) sensitization to 1 or more trees, grasses, and/or weeds confirmed by immunologic tests, such as SPT, and singleplex or multiplex specific IgE test(s); 3) symptoms of rhinitis, conjunctivitis, and/or asthma worsened after exposure to sensitized inhalant allergen(s); and 4) oropharyngeal symptoms (itchiness or swelling of the mouth, face, lip, tongue, and throat during certain food ingestion) occurring after ingestion of fruits and vegetables for which a causal relationship of PFAS was already established. The food list contained common fruits and vegetables in South Korea, and it is described in **Table 1**. Patients who had fruit or vegetable allergy but whose symptoms did not satisfy the above criteria were diagnosed with true fruit or vegetable allergy. All diagnostic processes were conducted by allergy specialists.

Statistical analysis

The chi-squared test or Fisher's exact test was performed to evaluate the association between allergen groups. The Kruskal-Wallis one-way analysis of variance test was used to compare onset ages among different FA allergens. A P value of < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS software, version 23.0 (IBM Co., Armonk, NY, USA).

RESULTS

Demographics of the study population

Among 812 screened patients, 415 were diagnosed as having FA (**Table 2**). The mean age of FA patients was 38.5 years (range, 18–88 years). Three hundred twenty-two (77.8%) FA patients had comorbid allergic diseases. Among the comorbid allergic diseases, allergic rhinitis was the most common, comprising 222 (53.4%) of all patients. Cutaneous symptoms were the most common, which resulted in an initial visit to the Allergy Asthma Center (264, 63.6%), and a majority of patients (344, 82.8%) visited the hospital via the outpatient clinic.

Clinical manifestations of FA

Skin manifestation (287, 69.1%) was the most common symptom of FA patients, followed by oral, cardiovascular, respiratory, gastrointestinal, and nasal symptoms. Most symptoms (394, 95.0%) occurred within 1 hour of exposure, but 21 (5.0%) patients showed a delayed response (at least 1 hour) after food ingestion. Among the FA patients, 155 (37.3%) were diagnosed with PFAS, 20 (3.4%) were diagnosed with FDEIA, and 8 (3.6%) were diagnosed with red meat (α-Gal) allergy (**Fig. 1**). All FDEIA cases were due to wheat allergy.

Of the FA patients with PFAS, 97 (62.9%) showed mild symptoms, and 20 (12.9%) experienced anaphylactic symptoms. In FA patients without PFAS, 109/261 (41.7%) were also diagnosed as having anaphylaxis.

Number of causative food allergens and associations between causative allergen groups

More than half of the total subjects exhibited multiple allergies to foods (238/415 cases, 57.3%), and the average number of causative allergens was 2.39. Sorted by categories, fruit (189 patients) was the most frequent causative food allergen group, followed by seafood (117 patients), grains and legumes (119 patients), and nuts and seeds (60 patients).Among fruits, apples, peaches, and

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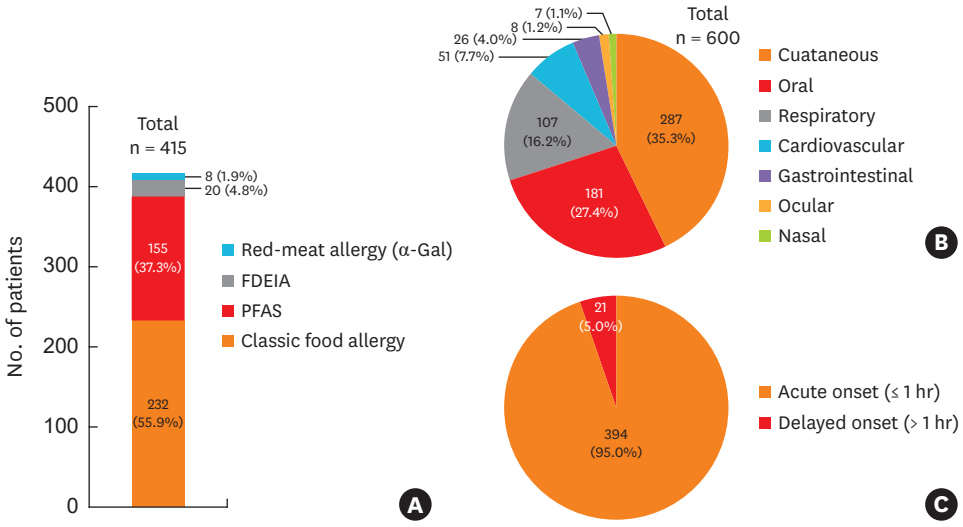

Fig. 1. Proportion of food allergy subtypes and symptom manifestations: (A) food allergy subtypes, (B) symptom manifestations, and (C) symptom onset.
α-Gal, galactose-α-1,3-galactose; FDEIA, food dependent exercise induced anaphylaxis; PFAS, pollen food allergy syndrome.

plums were the most common allergen causative allergens (163/189, 86.2%). Among seafood, allergic events due to crustaceans (111/117, 94.8%) were overwhelmingly higher than those due to other seafood; only 6 patients had both fish and shellfish allergies.

In other groups, wheat (63 patients), peanut (31 patients), soybean (27 patients), walnut (25 patients), almond (23 patients), watermelon (20 patients), milk (8 patients), and egg (6 patients) caused allergic events. Additionally, few allergic events to unique, Korean food-

Table 2. Clinical characteristics of study patients

Characteristics	No. (%) of patients (n = 415)
Sex, No. (%)	
Male	211 (51.0)
Female	214 (49.0)
Mean age (year ± standard deviation)	38.5 ± 15.0
Comorbidities, No. (%)	
Asthma	58 (14.0)
Allergic rhinitis	222 (53.4)
Allergic conjunctivitis	69 (16.6)
Atopic dermatitis	26 (6.3)
Chronic urticaria	131 (31.5)
Laboratory findings	
Total eosinophilic count (per μL)	233.3 ± 301.2
Total immunoglobulin E (kU/L)	623.3 ± 982.0
Route of visit, No. (%)	
Outpatient clinic	344 (82.7)
Emergency room	71 (17.1)
First visit symptoms, No. (%)	
Cutaneous	264 (63.6)
Respiratory	159 (38.2)
Nasal	116 (27.9)
Oral	68 (16.3)
Ocular	52 (12.5)
Cardiovascular	38 (9.1)
Gastrointestinal	22 (5.3)

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specific allergens (*doraji*, ginseng, and *sseumbagui*) were observed. The detailed results of the FA events are shown in **Fig. 2**.

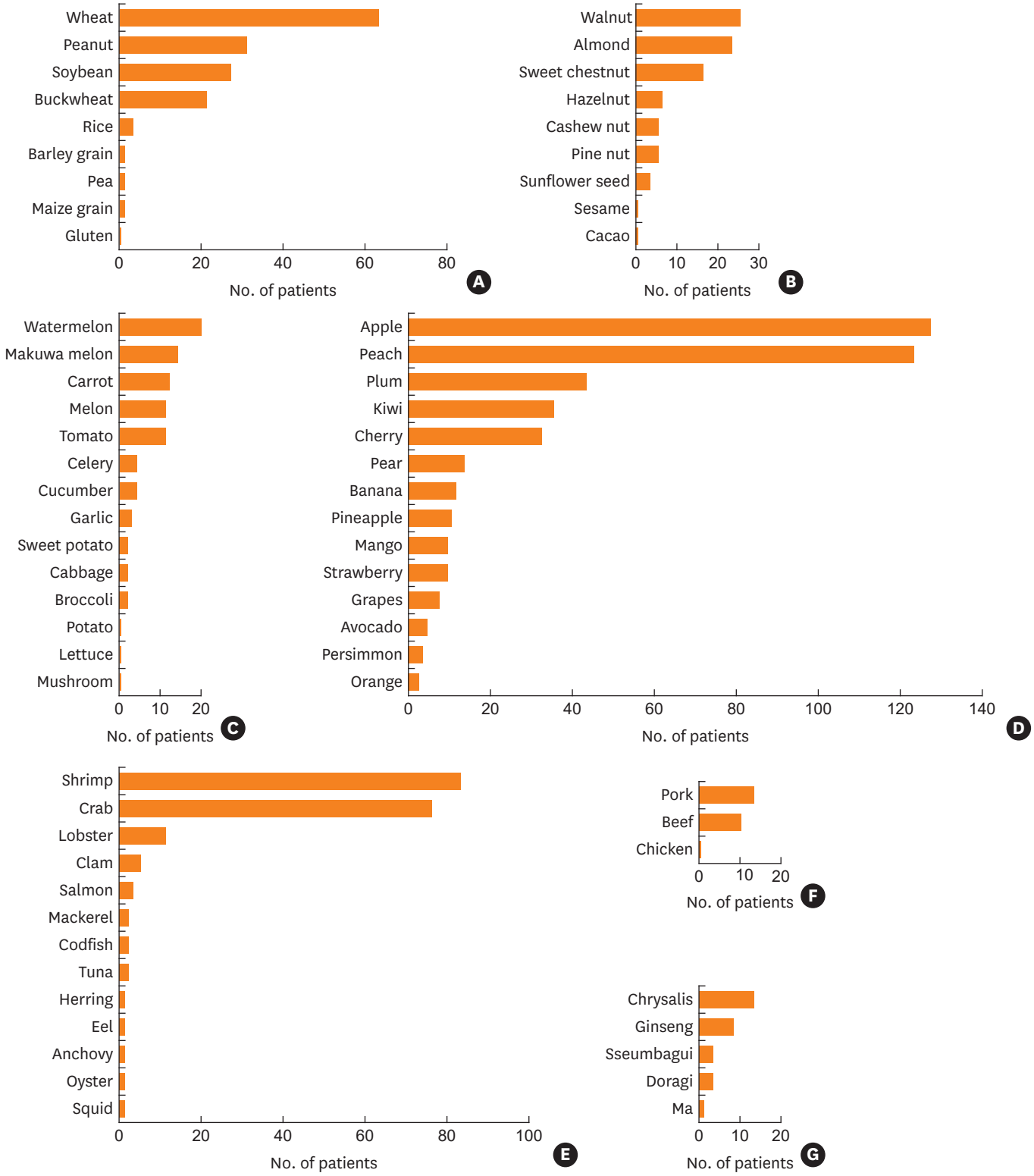

Fig. 2. Frequency of food allergens categorized by derivation: (A) grains and legumes, (B) nuts and seeds, (C) other vegetables, (D) fruits, (E) seafood, (F) meat, and (G) other.

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Table 3. Relationships between allergen groups

Groups	Wheat and buckwheat (n = 79)	Other grains and legumes (n = 51)	Nuts and seeds (n = 57)	Fruits (n = 189)	Other vegetables (n = 60)	Crustaceans (n = 111)	Other seafood (n = 12)	Red meat (n = 15)	Dairy foods (n = 13)	Silkworm pupa (n = 13)	Other (n = 15)
Wheat and buckwheat	-	11 (21.5)	6 (10.5)	5* (2.7)	5 (8.3)	12* (10.8)	1 (8.3)	0 (0.0)	2 (15.4)	1 (7.7)	1 (7.7)
Other grains and legumes	11 (13.9)	-	17* (29.8)	37* (19.6)	9 (15.0)	5* (4.5)	2 (16.7)	0 (0.0)	3 (23.1)	0 (0.0)	6 (46.2)
Nuts & seeds	6 (7.6)	17* (33.3)	-	36* (19.1)	14* (23.3)	6* (5.4)	1 (8.3)	0 (0.0)	3 (23.1)	1 (7.7)	6* (46.2)
Fruits	5* (6.3)	37* (72.5)	36* (63.1)	-	48* (80.0)	10* (9.0)	7 (58.3)	0* (0.0)	1* (7.7)	2* (15.4)	13* (86.7)
Fruits with PFAS	3* (3.8)	28* (54.9)	32* (56.1)	146* (77.3)	46* (76.7)	7* (6.3)	7 (58.3)	0* (0.0)	0 (0.0)	1* (7.7)	10* (66.7)
Genuine fruits	2* (2.5)	9 (17.7)	4 (7.0)	43 (22.8)	2 (3.3)	3* (2.7)	0 (0.0)	0 (0.0)	1 (7.7)	1 (7.7)	3 (20.0)
Other vegetables	5* (6.3)	9 (17.6)	14* (24.6)	48* (25.4)	-	1 (0.9)	2 (16.7)	0 (0.0)	0 (0.0)	1 (7.7)	7* (53.9)
Crustaceans	12* (15.2)	5* (9.8)	6* (10.5)	10* (5.3)	1 (1.7)	-	5 (38.5)	0 (0.0)	1 (7.7)	6 (46.2)	1 (7.7)
Other seafoods	1 (1.3)	2 (3.9)	1 (1.7)	7 (3.7)	2 (3.3)	5 (4.4)	-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Red meat	0 (0.0)	0 (0.0)	0 (0.0)	0* (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	1 (7.7)	0 (0.0)	0 (0.0)
α-Gal allergy	0 (0.0)	0 (0.0)	0 (0.0)	0* (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8* (53.3)	1 (7.7)	0 (0.0)	0 (0.0)
Genuine pork or beef	0 (0.0)	0 (0.0)	0 (0.0)	0* (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7* (46.7)	0 (0.0)	0 (0.0)	0 (0.0)
Dairy foods	2 (2.5)	3 (5.9)	3 (5.3)	1* (0.5)	0 (0.0)	1 (0.9)	0 (0.0)	1 (6.7)	-	0 (0.0)	0 (0.0)
Silkworm pupa	1 (1.3)	0 (0.0)	1 (1.7)	2* (1.1)	1 (1.7)	6 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	-	1 (7.7)
Others	1 (1.3)	6 (11.8)	6* (10.5)	13* (6.9)	7* (12.7)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	-

Values are presented as number of cases (%). Overlapping cases among different allergen groups were measured and analyzed to compare their relevance.
PFAS, pollen-food allergy syndrome; α-Gal, galactose-α-1,3-galactose.
*$P < 0.05$, P value was calculated using the χ^2 test or Fisher's exact test. Asterisk means that patients who have sensitization to certain allergens tend to be sensitive to another allergen.

The associations between food allergen groups are described in **Table 3**. Of 79 FA patients who were allergic to wheat and buckwheat, 12 (10.8%) also exhibited crustacean allergy ($P = 0.010$). One-third of FA to other legumes and grain showed concurrent FA to nuts and seeds ($P < 0.001$). Most allergen groups were significantly associated with fruit allergy ($P < 0.001$).

Anaphylaxis proportion between allergen groups

Of 415 FA patients, 129 (31.0%) were diagnosed as having anaphylaxis. Wheat (39, 30.2%) was the most common causative allergen for anaphylaxis. The proportion of anaphylaxis occurrence was also the highest for wheat (39/63, 61.9%), followed by buckwheat (8/31, 25.8%), crustacean (34/111, 30.6%), and α-Gal allergy (4/8, 50.0%). The number of anaphylaxis cases was high in fruits, but its proportion to total allergic cases (33/189, 17.4%) was lower compared to that of other groups (**Fig. 3**).

Difference in causative allergens based on age and sex

There was no sex difference in the majority of allergens, except wheat, buckwheat, red meat (α-Gal), and dairy foods. Wheat and buckwheat allergy were more frequently observed in male patients, whereas red meat and dairy allergy were more frequently observed in female patients. With regard to age, allergy to grains and legumes was significantly more frequent in younger patients. However, patients with red meat allergy due to α-Gal tended to be older than those with other allergies, with a mean age of 70.3 years (**Table 4**).

DISCUSSION

As there are few previous studies regarding Korean adult FA epidemiology, this study is important.[1,14] Moreover, as commonly consumed foods and environmental factors are rapidly changing, previous epidemiologic studies do not necessarily represent the current status.[1,21] Furthermore, country-specific patterns of food consumption widely differ; therefore, Western studies do not reflect actual causative allergens in Korean FA.[5,22,23] For instance, buckwheat consumption is significantly higher in Eastern Asian populations than in Western

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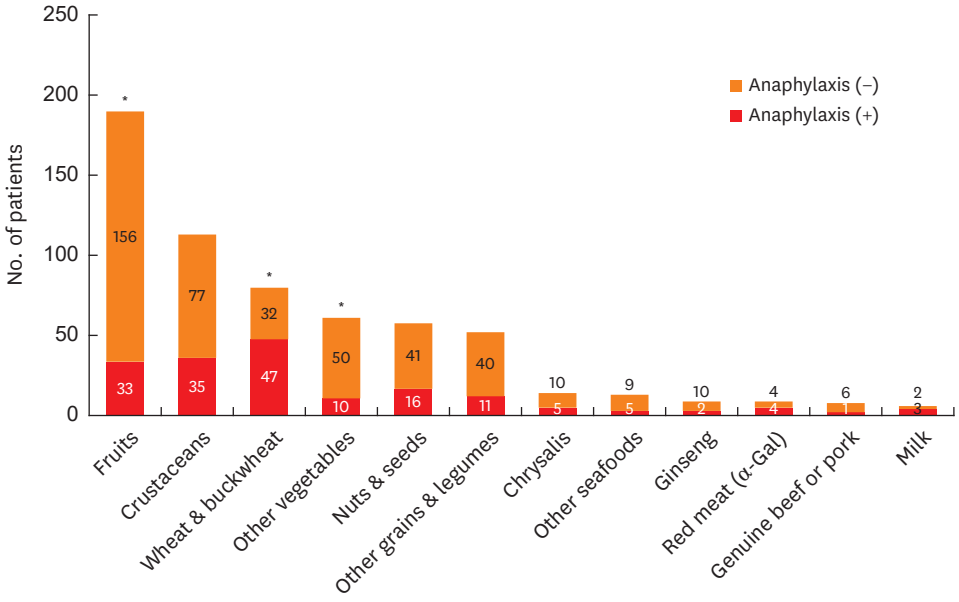

Fig. 3. Proportion of anaphylaxis among food allergy patients.
α-Gal, galactose-α-1,3-galactose.
*P value < 0.05.

populations. In addition, there are several unique food materials that can provoke allergic hypersensitivity reactions; such foods include ginseng, silkworm pupa (chrysalis), and vegetables such as *doraji*, *ma*, and *sseumbagui*.

There were clear differences in causative foods based on previous results of the food sensitization pattern as determined using the SPT.[12] Concerning fish allergens, a previous SPT survey revealed sensitivity ranging from 0.7% to 11.9%, but such patients were rare in the current study. Moreover, silkworm pupa, which previously showed the highest sensitization patterns, had a relatively low proportion among symptomatic patients, which suggests that skin testing for sensitivity to silkworm pupa has a high false-positive rate.[24]

Table 4. Differences in causative allergens by age and sex

Allergen groups	Male					Female					Total
	< 30 yr	30–49 yr	50–69 yr	≥ 70 yr	Total	< 30 yr	30–49 yr	50–69 yr	≥ 70 yr	Total	
Wheat and buckwheat	11 (22.4)	19 (38.8)	14 (28.6)	5 (10.2)	49 (62.0)	7 (23.3)	18 (60.0)	5 (16.7)	0 (0.0)	30 (38.0)	79
Other grains and legumes	16 (61.5)	5 (19.2)	4 (15.3)	1 (3.8)	26 (50.9)	7 (28.0)	8 (32.0)	8 (32.0)	2 (8.0)	25 (49.1)	51*
Nuts and seeds	17 (58.6)	10 (34.5)	2 (6.9)	0 (0.0)	29 (50.8)	10 (35.7)	12 (42.9)	5 (17.9)	1 (3.5)	28 (49.2)	57
Fruits	43 (46.7)	36 (39.1)	11 (12.0)	2 (2.2)	92 (48.6)	29 (29.9)	37 (38.1)	28 (28.9)	3 (3.1)	97 (51.4)	189*
Fruits with PFAS	33 (44.6)	30 (40.5)	10 (13.5)	1 (1.4)	74 (50.7)	23 (31.9)	28 (38.9)	20 (27.8)	1 (1.4)	72 (49.3)	146*
Genuine fruits	10 (55.6)	6 (33.3)	1 (5.6)	1 (5.6)	18 (41.9)	6 (24.0)	9 (36.0)	8 (32.0)	2 (8.0)	25 (58.1)	43
Other vegetables	9 (37.5)	12 (50.0)	2 (8.3)	1 (4.2)	24 (40.0)	9 (25.0)	16 (44.4)	8 (22.2)	3 (8.3)	36 (60.0)	60
Crustaceans	16 (28.6)	33 (58.9)	6 (10.7)	1 (1.7)	56 (50.0)	18 (32.1)	26 (46.4)	11 (19.6)	1 (1.8)	56 (50.0)	112
Other seafood	2 (40.0)	1 (20.0)	2 (40.0)	0 (0.0)	5 (38.5)	1 (12.5)	5 (62.5)	2 (25.0)	0 (0.0)	8 (61.5)	13
Red meat	1 (16.7)	0 (0.0)	2 (33.3)	3 (50.0)	6 (40.0)	2 (22.2)	4 (44.4)	0 (0.0)	3 (33.3)	9 (60.0)	15*
α-Gal allergy	0 (0.0)	0 (0.0)	1 (12.5)	3 (37.5)	4 (50.0)	0 (0.0)	1 (25.0)	0 (0.0)	3 (75.0)	4 (50.0)	8*
Genuine pork or beef	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	2 (28.6)	2 (40.0)	3 (60.0)	0 (0.0)	0 (0.0)	5 (71.4)	7
Dairy foods	2 (66.7)	0 (0.0)	1 (33.3)	0 (0.0)	3 (25.0)	2 (22.2)	5 (55.6)	2 (22.2)	0 (0.0)	9 (75.0)	12
Silkworm pupa	1 (16.7)	5 (83.3)	0 (0.0)	0 (0.0)	6 (46.1)	0 (0.0)	4 (57.1)	1 (14.3)	2 (28.6)	7 (53.9)	13*
Others	2 (33.3)	4 (66.7)	0 (0.0)	0 (0.0)	6 (40.0)	2 (22.2)	2 (22.2)	4 (44.4)	1 (11.1)	9 (60.0)	15

Values are presented as number of cases (%).
*P < 0.05, P value was calculated using the chi-squared test or Fisher's exact test. Asterisk means that food allergy frequencies have significant relationship with age groups.
PFAS, pollen-food allergy syndrome; α-Gal, galactose-α-1,3-galactose.

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The precise diagnosis of FA requires a double-blind, placebo-controlled, food challenge (DBPCFC) test as a confirmatory test; however, there are difficulties in conducting DBPCFC clinically. Accordingly, in the present study, we used the revised version of the Bradford and Hills criteria, which is valuable for causality assessment in epidemiologic fields. Crucial evidence needed for diagnosis of adult FA should include plausible clinical manifestations, temporal relations between exposure and symptoms onset, and as well as specificity and reproducibility of clinical symptoms, and/or relationship between physical activities, and presence of suspected food specific IgE.[25] These clues are more informative in adult patients than in pediatrics. In pediatric FA, it is difficult to judge the temporal relationship between de-challenge or re-challenge of causative food and symptom expression. In addition, the fluctuating nature of atopic dermatitis symptoms makes it difficult for clinicians to confirm the causative allergen.[26,27] However, in adult FA, the main symptoms are urticaria, angioedema, itching sensation at the exposed area, and anaphylaxis. Therefore, it is easier to distinguish the causative food based on detailed history taking and laboratory testing.

Generally, the management of adult FA encompasses the avoidance of causative allergens and prompt treatment of allergic reactions.[28,29] In contrast, in pediatric FA, the allergy can be remitted naturally by avoiding the causative allergens; additionally, there are emerging treatments such as oral immunotherapy for specific FAs.[30,31] However, in adults, FA remission is unusual, and FAs are considered long-lasting.[32] Furthermore, the efficacy of oral immunotherapy in adult FA is ambiguous.[33] Accordingly, clear identification of common causative food allergens is more meaningful in adults.

The spectrum of individual FA symptoms in adults is also variable and includes mild urticaria, itching, angioedema, and anaphylaxis. It is noteworthy that almost one-third of FA patients in the current study were diagnosed as having anaphylaxis, suggesting that food allergens are an important cause of anaphylaxis in Korean adults. Moreover, similar to the results of another study, our data showed that wheat and seafood (especially crustaceans) were a leading cause of food-induced anaphylaxis.[11] However, seafood led to anaphylactic reactions less frequently than did wheat or buckwheat. The proportion of anaphylaxis induced by α-Gal allergy was also high. Therefore, patients who have allergies to crustaceans, wheat, buckwheat, and red meat more frequently experience severe allergic symptoms, including anaphylaxis. The most characteristic feature of IgE-mediated allergic reaction is immediate response without delay. However, in case of FDEIA or red meat allergy due to α-Gal allergy, allergic symptoms are usually delayed or occur concomitantly with a specific physical condition (*e.g.,* exercise after meal). Consequently, specific and detailed questionnaires are needed to make an appropriate diagnosis.

Unlike other epidemiologic studies done in Korea, our study consisted of a large number of PFAS patients.[11] One-third of FA patients had accompanying PFAS, which is believed to have been affected by the high coexistence of AR in the FA. Kim *et al.*[14] previously reported that 96.2% cases of FA among birch pollinosis patients were PFAS. Our study also showed 94.8% of PFAS patients had accompanying AR. Among the PFAS patients, 85.8% of patients were sensitized to Fagales tree pollens, which include birch and oak trees, and they have strong cross-reactivity; this was followed by mugwort (38.3%), ragweed (37.0%), Hop Japanese (34.4%), and grass species (14.3% to 16.9%) (**Supplementary Table 1**).[34] Common causative foods according to the pollen type were slightly different; apple (69.4%), peach (63.3%), plum (18.4%), kiwi (16.3%), peanut (14.3%), cherry (14.3%), pear (12.2%), almond (10.2%), watermelon (10.2%), and carrot (10.2%) were frequent causative allergens in tree pollen

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sensitized PFAS patients. Furthermore, for these Fagales pollen-sensitized PFAS patients, we have described the sufficient effect of subcutaneous immunotherapy with Fagales pollen.[35] The trends regarding causative foods of PFAS according to sensitized pollen were similar to a recent nationwide study in Korea that apple, peach, plum, and kiwi were the most common causative foods in PFAS with tree pollen sensitization (**Supplementary Table 2**).[13]

In addition, it is worth noting that more than half of the patients have multiple culprit allergens. The number of causative food allergens is one of the largest differences in FA between adults and children. Previous studies showed relatively lower percentages of multiple causative allergens in pediatric FA patients.[36,37] Unlike pediatric FA patients, adult FA patients have a greater rate of PFAS and more specific subtypes of FA, such as red meat allergy due to α-Gal sensitization or crustaceans. In the clinical manifestation, overall symptoms of PFAS patients were mild; however, one-third of them initially visited the allergy clinic due to respiratory symptoms or anaphylaxis. Generally, PFAS is classified as a class II FA, which results from sensitization to cross-reacting aeroallergens, and symptoms are usually mild. However, our results suggest that 12% of FA patients with PFAS also experience anaphylaxis; hence, these conditions should be checked and managed carefully. In addition, when compared to classical (type I) FA patients, causative allergens of PFAS are multiple and are derived from a wider variety of fruits and vegetables. Hence, a detailed history taking of the presence of comorbid allergic disease is necessary. These factors may explain why our results showed a higher proportion of PFAS and fruit allergy rather than crustaceans or wheat as causative allergens, compared to a prior epidemiologic study.[11]

With respect to age, α-Gal allergy is more notable than other FAs. In the present study, all α-Gal allergy patients were at more than 50 years of age, which is similar to the findings of previous cohort studies.[38,39] However, it is still unknown why older individuals tend to exhibit more allergies to α-Gal. Unlike other food allergens, IgE sensitization to α-Gal is associated with dietary habits and environmental factors, such as tick bite.[40] These factors may differ by age; nonetheless, further research is needed.

This study is important because regulations should reflect the real situation rather than public opinion or perception. Every year, the Korea Food & Drug Administration (KFDA) publishes a guidebook of FA for educational purposes, and it lists chicken among the common causative food allergens. The KFDA also issued an announcement concerning labeling of food materials (KFDA announcement 2018-108); the announcement proclaimed that chicken and squid should be labeled on any manufactured food stuffs. However, in our study, no adult patients were allergic to chicken or squid; thus, revision of the regulation should be considered.

In addition, most literature regarding FA has focused on classic food allergens and on pediatric FA patients. Recently, there have been significant advances in understanding allergic mechanisms and causative allergens, especially those for FDEIA, PFAS, and α-Gal allergy. With improvements in molecular technology, component resolved diagnosis has emerged as a major breakthrough in FA diagnosis; this approach improves diagnostic accuracy without use of the laborious DBPCFC test. This may negate the consideration of previous epidemiologic studies regarding FA. The present study adopted recent advances, and there was a sufficient number of enrolled patients to conduct a cross-sectional study. Therefore, we believe that this study could serve as a reference for further FA epidemiologic studies in Korea.

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There are several limitations to this study. There might be a selection bias with regard to disease severity, because this study was conducted in a single tertiary institute. This may explain the higher proportion of anaphylaxis compared to previous epidemiologic studies; hence, the severity of FA can vary among different practice settings.[11,12] Another limitation may be that we did not conduct a DBPCFC test as recommended as an AAAAI/ACAAI allergy practice parameter for FA.[25]

In conclusion, clinical features and causative foods of adult FA in Korea are diverse and differ from those in children. Wheat, fruits, crustaceans, and red meat (α-Gal) may induce anaphylaxis more frequently in adults, and we suggest that more attention should be given to these differences.

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SUPPLEMENTARY MATERIALS

Supplementary Table S1

Sensitization rate of pollen allergens in food allergy patients with pollen food allergy syndrome

Click here to view

Supplementary Table S2

Causative foods of pollen food allergy syndrome in pollen-sensitized patients

Click here to view

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